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Synthesis of Indenes by the Palladium-Catalyzed Carboannulation of Internal Alkynes

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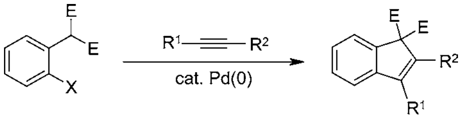
ABSTRACT



E = CO_2Et, CN, SO_2Ph; X = Br, I

A number of highly substituted indenes have been prepared in good yields by treating functionally substituted aryl halides with various internal alkynes in the presence of a palladium catalyst. The reaction is believed to proceed by regioselective arylpalladation of the alkyne and subsequent nucleophilic displacement of the palladium in the resulting vinylpalladium intermediate.

The indene ring system is present in drug candidates possessing interesting biological activities[1] and metallocene complexes utilized to catalyze olefin polymerization.[2] The importance of indenes has stimulated the development of a number of approaches for the synthesis of the indene ring system, including the reduction/dehydration of indanones,[3] the cyclization of phenyl-substituted allylic alcohols,[4] and the ring expansion of substituted cyclopropenes.[5] Although these classic methods are quite effective for the synthesis of simple indenes, they have certain drawbacks in the preparation of highly substituted indenes, such as the strong acid medium required, the lengthy reaction sequences involved and the low tolerance for functionality. These drawbacks have prompted us to develop a general synthesis of indenes utilizing palladium-catalyzed annulation methodology.

The palladium-catalyzed annulation of alkynes has proven to be extremely effective for the synthesis of a wide variety of carbocycles and heterocycles.[1] For example, we have successfully employed this annulation chemistry for the synthesis of indoles,[6] benzofurans,[7] isocoumarins,[8] isoquinolines,[9] carbolines,[10] indenones[11] and polycyclic aromatic hydrocarbons.[12] The palladium-catalyzed synthesis of these carbocycles and heterocycles has tremendous advantages over traditional annulation methods. For example, only catalytic amounts of palladium are employed, a wide number of important organic functional groups are readily tolerated, and the palladium catalyst is quite stable to air and moisture.

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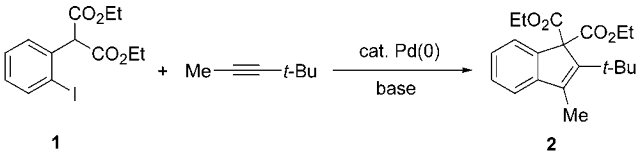
Furthermore, the base-promoted Pd-catalyzed annulation of alkynes is especially useful for preparing acid-sensitive substances, such as indenes.[13] We herein wish to report a new synthesis of indenes by the palladium-catalyzed carboannulation of internal alkynes by functionally substituted aryl halides.

Initial studies were aimed at finding the optimal reaction conditions for the palladium-catalyzed carbonannulation of internal alkynes. Our investigation began with the reaction of diethyl (2-iodophenyl)malonate (**1**) and 4,4-dimethyl-2-pentyne (**2**) (Scheme 1). The reaction was first attempted using 1 equiv of diethyl (2-iodophenyl)malonate (**1**) (0.25 mmol), 5 equiv of 4,4-dimethyl-2-pentyne, 5 mol % of $Pd(OAc)_2$ as the catalyst, 1 equiv of n-Bu_4NCl, and 2 equiv of KOAc in 1 mL of DMF at 80 °C. This reaction provided a 49% yield of the desired indene **2** in 24 h with a small amount of material which appeared to arise by multiple insertion of the alkyne. To minimize the formation of the multiple-insertion products, the concentration of the reactants was lowered by employing 5 mL of DMF as the solvent. This reaction furnished an 86% yield of the indene product without any side products, but the reaction took 48 h to reach completion.

Scheme 1



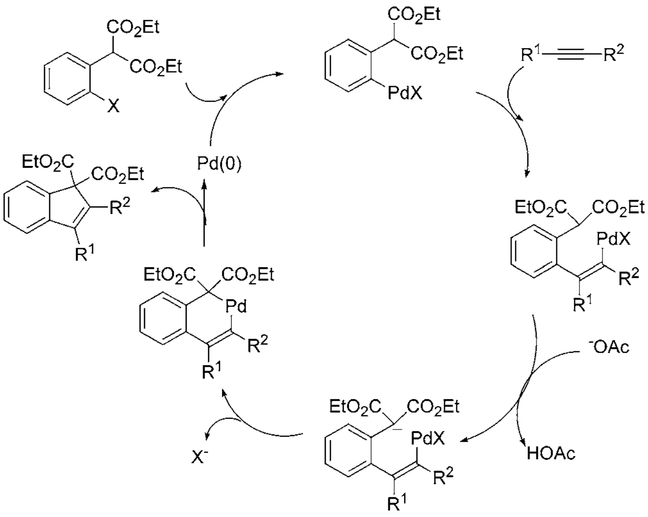
Using 5 mol % of PPh_3 as a ligand in this reaction did not increase the yield of the desired product. The use of other bases, such as K_2CO_3, Na_2CO_3, or organic amine bases, drastically reduced the yield of the desired product. Other Pd catalysts, such as $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ and $Pd_3(dba)_2 \cdot CHCl_3$, have also been employed in this annulation reaction. None of them gave a higher yield than $Pd(OAc)_2$. LiCl was examined as an alternative to n-Bu_4NCl, and the yield was comparable to the corresponding reaction using n-Bu_4NCl. When less than 5 equiv of 4,4-dimethyl-2-pentyne were used, the reactions were slower and the yields were lower, presumably due to the extreme volatility of this alkyne.

On the basis of the above optimization efforts, the combination of 1 equiv of diethyl (2-iodophenyl)malonate (**1**) (0.25 mmol), 5 equiv of internal alkyne, 5 mol % of $Pd(OAc)_2$, 1 equiv of n-Bu_4NCl, and 2 equiv of KOAc in 5 mL of DMF at 80 °C for 2 d gave the best result (Table 1, entry 1). Having gained an understanding of the factors that influence the carboannulation process, we explored the scope and limitation of this method. Further carboannulation results are summarized in Table 1.

The reactions of **1** with symmetrical alkynes, such as 4-octyne and diphenyl acetylene, afforded good yields of the desired products (entries 2 and 3). The annulation process is highly regioselective for alkynes containing tertiary alkyl, trimethylsilyl, or phenyl groups, yielding a single regioisomer with the more sterically demanding group in the 2-position of the indene ring (entries 1 and 4−6). The assignment of regiochemistry is based on analogy with our earlier indole work.[7] In the case of entry 5, a much lower yield (40%) of the indene product was isolated when KOAc was used rather than K_2CO_3.

This process tolerates considerable functionality. For example, the reaction of **1** with 3-phenyl-2-propyn-1-ol afforded a 51% yield of a single regioisomer (entry 6). The reactivity of other functionally substituted aryl halides has also been examined. Aryl halides bearing two electron-donating groups, such as **8**, still work well with 4,4-dimethyl-2-pentyne, affording 74% of the desired indene product (entry 7). Interestingly, when aryl bromide was employed, a 46% yield of the corresponding indene can be obtained (entry 8). Meanwhile, aryl halides with different electron-withdrawing groups have also been allowed to react with various internal alkynes to afford moderate yields of the desired products (entries 9−11). Several bases, such as KOAc, NaOAc, K_2CO_3 and Na_2CO_3, have been employed in these reactions and K_2CO_3 gave the highest yield of the desired annulation products.

Scheme 2



The mechanism shown in Scheme 2 is proposed for this annulation process. It consists of the following key steps: (1) oxidative addition of the aryl halide to the Pd(0) catalyst, (2) arylpalladium coordination to the alkyne and subsequent insertion of the alkyne to form a vinylic palladium intermediate, (3) generation of a carbanion by the base, (4) intramolecular nucleophilic attack of the carbanion on the vinylic palladium intermediate to afford a palladacyclic intermediate, and (5) reductive elimination of the

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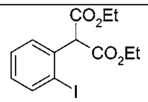
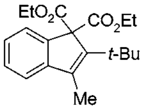
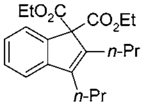
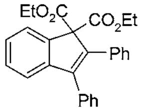
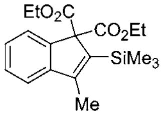
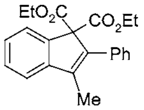
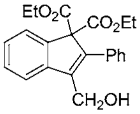
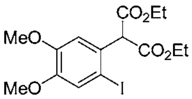
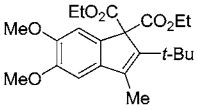
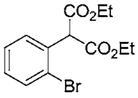
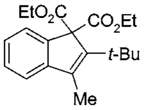
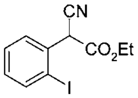
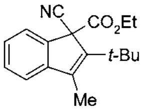
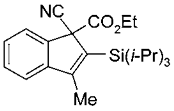
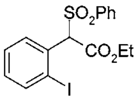
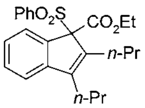
Table 1. Palladium-catalyzed Carboannulation of Internal Alkynes by Aryl Halides[a]

entry	halide		alkyne	product		% isolated yield
1		(**1**)	$\mathrm{Me}-\equiv-t\text{-}\mathrm{Bu}$		(**2**)	86
2[b]		(**1**)	$n\text{-}\mathrm{Pr}-\equiv-n\text{-}\mathrm{Pr}$		(**3**)	72
3[c]		(**1**)	$\mathrm{Ph}-\equiv-\mathrm{Ph}$		(**4**)	70
4[d]		(**1**)	$\mathrm{Me}-\equiv-\mathrm{SiMe_3}$		(**5**)	81
5[b]		(**1**)	$\mathrm{Me}-\equiv-\mathrm{Ph}$		(**6**)	63
6[b]		(**1**)	$\mathrm{HOCH_2}-\equiv-\mathrm{Ph}$		(**7**)	51
7		(**8**)	$\mathrm{Me}-\equiv-t\text{-}\mathrm{Bu}$		(**9**)	74
8		(**10**)	$\mathrm{Me}-\equiv-t\text{-}\mathrm{Bu}$		(**2**)	46
9[b,d]		(**11**)	$\mathrm{Me}-\equiv-t\text{-}\mathrm{Bu}$		(**12**)	65
10[b,d]		(**11**)	$\mathrm{Me}-\equiv-\mathrm{Si}(i\text{-}\mathrm{Pr})_3$		(**13**)	52
11[b,d]		(**14**)	$n\text{-}\mathrm{Pr}-\equiv-n\text{-}\mathrm{Pr}$		(**15**)	45

[a] The reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the aryl halide, 1.25 mmol of the alkyne, 5 mol % of $\mathrm{Pd(OAc)_2}$, 0.25 mmol of $n\text{-}\mathrm{Bu_4NCl}$, 0.50 mmol of KOAc stirred in 5 mL of DMF at 80 °C under an N_2 atmosphere for 48 h. [b] 0.25 mmol of LiCl was used instead of $n\text{-}\mathrm{Bu_4NCl}$. [c] 0.50 mmol of the alkyne was used. [d] 0.50 mmol of $\mathrm{K_2CO_3}$ was used instead of KOAc.

intermediate to furnish the indene and regenerate the Pd(0) catalyst.

The oxidative addition of aryl halides to Pd(0) is well-known and integral to a wide variety of Pd(0)-catalyzed processes.[14] Subsequent *syn*-addition of the arylpalladium compound to the alkyne has also been established for the analogous palladium-catalyzed hydroarylation process[15] and assumed in many other alkyne insertion processes.[16] The high regioselectivity for unsymmetrical alkynes is probably due

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[14] Rodd, E. H. *Chemistry of Carbon Compounds*; Elsevier: Amsterdam, 1954; Vol. III, p 82.

to the steric hindrance present in the developing carbon−carbon bond. Alkyne insertion occurs so as to generate the least steric strain in the vicinity of the shorter developing carbon−carbon bond, rather than the longer carbon−palladium bond (Figure 1).

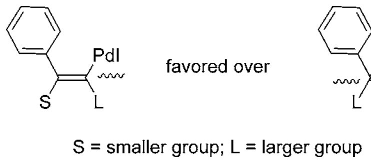

Figure 1. Steric effects on the regiochemistry of alkyne insertion.

Analogous regiochemistry is also observed in all of our previously reported annulation chemistry.[6] The subsequent steps of this process are presumed to be palladacycle formation and subsequent reductive elimination. Although we have no actual proof of the intermediacy of such palladacycles, a closely related heterocyclic arylpalladium amide has been reported and shown to undergo analogous thermal reductive elimination to form the corresponding aromatic heterocycle.[17] It stands to reason that analogous carbon-containing palladacycles would behave similarly.

The reactions proceed under relatively mild reaction conditions and generally give good yields. This annulation process exhibits excellent regioselectivity and is particularly well suited for the synthesis of hindered 2-substituted indenes.

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Supporting Information Available: General experimental procedures and characterization data for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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